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Long term follow-up after endovascular brachytherapy of femoro-popliteal arteries

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Abstract. To perform a long term follow-up after endovascular brachytherapy (EVBT) and balloon angioplasty (PTA) regarding vessel patency and diameter. EVBT had been successfully used to decrease restenosis in short term, but long term data are lacking. Participants of a randomized study comparing EVBT and balloon angioplasty alone were invited for follow-up examination ten years after intervention. Using a standardized protocol measurement of the patency and vessel diameter was performed of femoral and popliteal arteries. 44 patients were included, 21 had been treated with EVBT and 23 had received PTA alone. Target lesion patency was similar between the two groups (90.5% vs. 87.0%). Vessel diameter of the target lesion was significantly greater in the EVBT group (6.4 mm, range 3.9–9.9) compared to the controls (5.0 mm, range 3.1–7.4; $p = 0.002$). Ten years after EVBT of femoro-popliteal arteries vessel diameter is significantly increased whereas patency rate is not different compared to angioplasty alone.

Keywords: Endovascular brachytherapy, femoro-popliteal artery, long term follow-up, duplex sonography, peripheral artery disease, aneurysm

1. Introduction

Long-term efficacy of endovascular brachytherapy (EVBT) for reducing restenosis after femoro-popliteal angioplasty (PTA) was rather disappointing despite promising results in early publications [13]. In a meta-analysis published in the International Journal of Surgery in 2012 six clinical trials comparing EVBT with PTA were included [14]. After 12 months a significant lower restenosisrate was reported, however the risk of developing new lesions was higher in the EVBT-group. No differences were found after 24 months. Late acute thrombotic occlusion after EVBT may compromise the benefit of endovascular radiation [1]. In a Swiss multicentre study (PAB-study) the effect of EVBT had been investigated in patients over 50 years of age with claudication Rutherford class II and III [5] For the EVBT a ^{192}Iridium (^{192}Ir) source was used and a dose of 14 Gy applied over the length of the lesion. The main finding of this study was that the restenosis rate was significantly reduced by six months.

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It is well known that radiation injury causes alterations in blood vessels, which are dose-dependent. High-dose radiation used for the treatment of malignant tumours may lead to accelerated arteriosclerosis occurring 10 to 20 years later but also to aneurysm formation [4, 16]. In EVBT for femoro-popliteal arteries slight dilations of the treated segments have been noted and also aneurysm formation was described after a relative short follow-up of 6 to 12 months [10]. In the Swiss PAB-study Probucol or placebo had been given in addition to the EVBT and/or PTA. Probucol, an antioxidant showed a positive effect on vascular lumen size in a porcine angioplasty model [18]. In clinical studies in coronary arteries the results are conflicting [3, 8, 15, 21]. In the PAB-study the additional treatment with Probucol did not affect the restenosis rate [5].

The goal of the present study was to investigate patency and vessel diameter of the femoral and popliteal arteries which had been treated with EVBT in the PAB Study at our centres ten years ago. To our knowledge, no such long follow-ups after EVBT of femoro-popliteal arteries are available in the literature.

2. Materials and methods

The Clinics for Angiology of the University Hospital Zurich and Basel had participated at a multicentre study testing the effect of endovascular brachytherapy and the additional use of Probucol compared to balloon angioplasty alone on restenosis in femoro-popliteal obstructions [5]. 148 patients had been included in "The PAB Randomized Multicentre Trial" in the two study centres. Since 2011 participants of the study had been invited for a follow-up examination. Sixty-nine patients (46.6%) were deceased, 20 patients (13.5%) were lost for follow-up (unknown address) and 15 patients (10.1%) were not able or not willingly to come for a follow-up visit (Fig. 1).

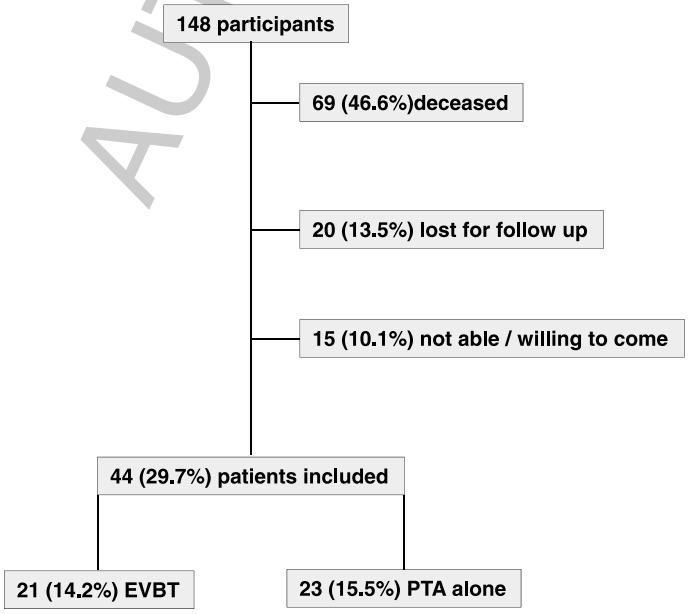

Fig. 1. Patient's selection.

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2.1. Initial intervention

Clinical data of theinitial intervention were extracted from the original case record forms of the PAB study. These data included cardiovascular risk factors, Fontaine classification of peripheral artery disease, ankle-brachial index (ABI) and information concerning the target lesion (localization, occlusion or stenosis, lesion length and stent implantation). Additional information regarding re-interventions was taken out of the electronic patient chart and from patient's history at the time of the follow-up visit.

2.2. Follow-up examination

A single investigator of each centre was blinded for clinical data and the type and localisation of the initial intervention. After measuring the ABI, a standardized Doppler colour coded duplex ultrasound (DUS) was performed by one experienced operator using a high-end ultrasound machine (logiq E9, GE Medical Systems AG, Glattbrugg, Switzerland or a Philips iU22 xMATRIX, Philips Healthcare, Best, Netherlands) with a linear transducer (L 9 MHz). A complete imaging of the femoro-popliteal arteries on both sides was performed using B-Mode and DUS with Doppler spectral analysis in all sections. Femoro-popliteal lesions were classified according the criteria of Jaeger et al. [7] normal vessel wall or slight wall thickening (<20%), atherosclerotic plaque with reduction of the vessel lumen less than 50%, prestenotic / intrastenotic ratio more than 2.5 (<70% stenosis), more than 3.5 (<99% stenosis) and complete occlusion (100%). The maximal external vessel diameter was measured in a longitudinal section in each part of the superficial femoral (proximal, middle and distal) and popliteal artery. Ectasia of the artery was arbitrary defined as a vessel diameter of more than 8 mm. Definition of a femoro-popliteal aneurysm was defined a vessel diameter larger than 1.0 cm as suggested elsewhere [24].

2.3. Statistical analysis

For statistical analysis StatView (SAS institute Inc.) was used. Continuous data are expressed as mean and range, nominal variables as frequencies and percentages. Comparisons between the EVBT and control group with respect to patient's characteristics and interventions were made using the unpaired *t*-test. Categoricalvariables were compared using Fisher's exact test. $P < 0.05$ was considered significant.

3. Results

Forty-four patients were eligible and included in the follow-up study between April 2011 and August 2014. 21 of them (age 65.1 years, 67% male) were in the former EVBT group and 23 did not receive radiation (age 67.3 years, 52% male). Patient's characteristics separated for both groups are shown in Table 1. Data of the initial intervention are listed in Table 2. Most interventions were performed in the middle and distal part of the superficial femoral artery. There were more stenoses (EVBT 71%, PTA 70%) than occlusions (EVBT 29%, PTA 30%) treated with a mean lesion length of 4.8 (range 0.5–20) cm in the EVBT group and of 4.4 (range 1–19) cm in the PTA group. Only one stent implantation was necessary in the EVBT group but none in the control group. After a mean follow-up time of 11.6 (range 8.8–15.1) and 11.9 (range 9.4–15.1) years respectively, secondary patency was 90.5% and 87.0% at the long termfollow-up (Table 3).

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Table 1
Baseline patients' characteristics

	EVBT ($n=21$)	PTA ($n=23$)
Age, years (range)	65.1 (36–78)	67.3 (48–82)
Male sex, *n* (%)	14 (66.7)	12 (52.2)
Mean weight, kg (range)	75.4 (58–105)	71.3 (45–105)
Mean height, cm (range)	170 (152–188)	165 (150–188)
Mean body mass index, kg/cm^2 (range)	25.9 (19.8–33.1)	25.8 (20.0–32.0)
Systolic blood pressure, mmHg (range)	147 (100–230)	147 (110–170)
Diastolic blood pressure, mmHg (range)	79 (52–90)	82 (75–105)
Cardiovascular risk factors		
Diabetes mellitus, *n* (%)	2 (9.5)	6 (26.1)
Hypertension, *n* (%)	13 (61.9)	19 (82.6)
Smoking, *n* (%)	14 (66.7)	9 (39.1)
Hyperlipidemia, *n* (%)	14 (66.7)	19 (82.6)
Rutherford classification		
Class II, *n* (%)	12 (57.1)	9 (39.1)
Class III, *n* (%)	9 (42.9)	14 (60.9)
Target lesion ABI (range)	0.73 (0.51–1.00)	0.72 (0.25–1.00)

Table 2
Initial intervention

	EVBT ($n=21$)	PTA ($n=23$)
Target lesion		
Superficial femoral artery, proximal part, *n* (%)	4 (19.0)	1 (4.3)
Superficial femoral artery, middle part, *n* (%)	6 (28.6)	9 (39.1)
Superficial femoral artery, distal part, *n* (%)	8 (38.1)	9 (39.1)
Popliteal artery, *n* (%)	3 (14.3)	4 (17.4)
Occlusions, *n* (%)	6 (28.6)	7 (30.4)
Stenoses, *n* (%)	15 (71.4)	16 (69.6)
Lesion length, cm (range)	4.8 (0.5–20)	4.4 (1–19)
Stentimplantation, *n* (%)	1 (4.8)	0 (0.0)

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Mean vessel diameter of the target lesion was 6.4 (range 3.9–9.9) mm significantly ($p=0.002$) greater in patients after EVBT compared to the legs of controls (5.0 mm, range 3.1–7.4 mm). An arterial ectasia defined as a diameter larger than 8 mm was documented in four (19%) patients (3 men) in the EVBT group, but was not found in the control group. Aneurysms were only found in three male patients after EVBT, one in the proximal superficial femoral artery (10.3 mm) and two in a non-treated popliteal artery (26.0 mm and 20.4 mm).

4. Discussion

In this long term follow-up study of patients treated with EVBT for femoro-popliteal obstructions a significant increase of the diameter of the treated artery was found by duplex ultrasound but no difference

Table 3
Long term follow-up

	EVBT ($n = 21$)	PTA ($n = 23$)	P
Age, years (range)	76.7 (50–91)	79.2 (60–92)	n.s.
Mean follow-up, years (range)	11.6 (8.8–15.1)	11.9 (9.4–15.1)	n.s.
Re-Intervention, *n* (%)	10 (47.6)	11 (47.8)	n.s.
Target lesion ultrasound			
No stenosis, *n* (%)	18 (85.7)	18 (78.3)	n.s.
Stenosis>50%, *n* (%)	1 (4.8)	2 (8.7)	n.s.
Occlusion, *n* (%)	2 (9.5)	3 (13.0)	n.s.
Mean target lesion diameter, mm (range)	6.4 (3.9–9.9)	5.0 (3.1–7.4)	0.002
Mean diameter contralateral, mm (range)	5.7 (3.5–7.4)	5.4 (4.4–6.8)	n.s.
Target lesion diameter >8 mm, *n* (%)	4 (19.0)	0 (0.0)	n.s.
Target lesion ABI (range)	0.73 (0.30–1.08)	0.75 (0.36–1.36)	n.s.

in secondary patency rate between the EVBT and angioplasty group and no difference in de-novo lesions was noted.

From a meta-analysis of the long-term outcome it was already known, that EVBT does not prevent medium- to late-term restenosis [14]. In the Vienna-2 study group the authors reported identical restenosis rates at 5 years with 72.5% in both groups [13, 17, 25]. Furthermore, the meta-analysis from Mitchell et al. suggests that EVBTsignificantly increases the risk of de novo stenosis elsewhere in thetreated artery but in this meta-analysis no data regarding vessel diameter are given [14].

In a small study the vessel lumen after PTA ($n = 10$) or PTA with EVBT ($n = 10$) was visualized using MRI [26]. Shortly after the intervention deep dissections had been detected and lumen area had almost doubled in both groups. At three months only in EVBT treated vessels some degree of dissection and further expansion of the vessel wall was found. Similar results were presented in studies using IVUS in femoro-popliteal arteries as well as in coronary arteries six months after the intervention [9, 12]. It might be that the delayed healing of the angioplasty-induced dissection triggers the further expansion of the vessel which is sustained even over ten years as suggested by our long-term follow-up study.

Although the positive remodelling might delay restenosis it has the potential risk of aneurysm formation in the long-term. Aneurysm formation in coronary arteries has already been reported in 1997 by Condado and colleagues in four of 20 patients treated with a single dose of radiation after a mean follow up of two years [2]. In our study population three patients developed an aneurysm after EVBT but none of the PTA treated patients. These aneurysms, however, were found also in non-treated vessels which may be an incidental finding, but even after ten years the mean vessel diameter at the site of EVBT was significantly larger in the brachytherapy than in the angioplasty group.

Still, the restenosis rate is not different probably due to the fact that radiation is not sufficient to inhibit neointimal formation. From experimental data it is suspected that irradiation of vascular cells may also induce profibrogenic cytokine synthesis and secretion, which could induce abnormal cell proliferation leading to fibrosis formation [6, 11, 19, 22, 23]. Radiation may induce and inhibit cell proliferation probably depending not only on the applied dose but also depending on the vessel wall characteristics like the amount of plaques or dissection. So far for femoro-popliteal angioplasty no benefit in the long-term regarding restenosis was shown but the potential risk of aneurysm formation could also be demonstrated in our study.

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A limitation of the study may be the relative small number of patients investigated in the follow-up, mainly caused by the mortality of nearly 50% within eleven years. Mortality risk in patients with peripheral arterial disease is known to be high, comparable to that of patients with myocardial infarction and ischemic stroke [20]. Thus, a certain selection bias may have influenced the excellent patency rate of the potential healthier survivors.

In summary, this first long term follow up study demonstrates a significant increase of vessel diameter after EVBT of femoro-popliteal arteries. Patients with former EVBT should undergo Duplex ultrasound to detect possible aneurysm formation of the treated artery.

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Declaration of conflicting interests

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